Intolerance to angiotensin converting enzyme inhibitors in asthma and the general population

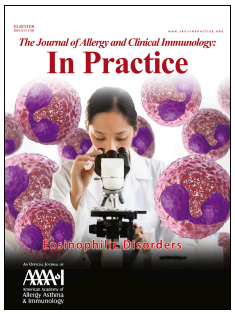
Morales, Daniel R.; Lipworth, Brian J.; Donnan, Peter T.; Wang, Huan

Published in:
The Journal of Allergy and Clinical Immunology: In Practice

DOI:
10.1016/j.jaip.2021.04.055

Publication date:
2021

Journal Pre-proof



Intolerance to angiotensin converting enzyme inhibitors in asthma and the general population: a UK population-based cohort study

Daniel R. Morales, PhD, Brian J. Lipworth, MD, Peter T. Donnan, PhD, Huan Wang, PhD

PII: S2213-2198(21)00561-4

DOI: https://doi.org/10.1016/j.jaip.2021.04.055

Reference: JAIP 3605

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 24 August 2020

Revised Date: 21 April 2021

Accepted Date: 22 April 2021

Please cite this article as: Morales DR, Lipworth BJ, Donnan PT, Wang H, Intolerance to angiotensin converting enzyme inhibitors in asthma and the general population: a UK population-based cohort study, *The Journal of Allergy and Clinical Immunology: In Practice* (2021), doi: https://doi.org/10.1016/j.jaip.2021.04.055.

Intolerance to angiotensin converting enzyme inhibitors in asthma and the general population: a UK population-based cohort study

Daniel R. Morales PhD, [1]Division of Population Health and Genomics, University of Dundee, UK. [2]Health Data Research (HDR)-UK Scotland. [3]Department of Public Health, University of Southern Denmark.

Brian J. Lipworth MD, Scottish Centre for Respiratory Research, University of Dundee, UK

Peter T. Donnan PhD, [1]Division of Population Health and Genomics, University of Dundee, UK. [2]Dundee and Epidemiology Biostatistics Unit, University of Dundee, UK

Huan Wang PhD, Division of Population Health and Genomics, University of Dundee, UK

Corresponding authors

Daniel R. Morales / Brian J Lipworth, Division of Population Health and Genomics, University of Dundee, Mackenzie Building, Kirsty Semple Way, Dundee, DD2 4BF. Tel: 01382 383475

Email: d.r.z.morales@dundee.ac.uk / b.j.lipworth@dundee.ac.uk

Short running title: Intolerance to ACE inhibitors in asthma

Word count: 2993

Funding/Conflict of interests

The project was supported by Tenovus (T15/59) that provided funded the role of HW. DM is supported by a Wellcome Trust Clinical Research Development Fellowship (Grant 214588/Z/18/Z). DM is a member of the European Medicines Agency Pharmacovigilance Risk Assessment Committee. BJL reports grants and personal fees from Sanofi, AstraZeneca, and Teva; reports personal fees from Cipla, Glenmark, and Lupin; reports grants, personal fees, and other from Chiesi, outside the submitted work.

ABSTRACT

Background: Angiotensin converting enzyme inhibitor (ACEI) intolerance commonly occurs requiring switching to an angiotensin-II receptor blocker (ARB). ACEI intolerance may be mediated by bradykinin potentially affecting airway hyper-responsiveness.

Objective: Assess the risk of switching to ARBs in asthma.

Methods: We conducted a new-user cohort study of ACEI initiators identified from electronic health records from the UK Clinical Practice Research Datalink. The risk of switching to ARBs in people with asthma, chronic obstructive pulmonary disease (COPD) and the general population were compared. Adjusted hazard ratios (HR) were calculated using Cox regression, stratified by British Thoracic Society (BTS) treatment step and ACEI type.

Results: Of 642,336 new-users of ACEI, 6.4% had active asthma. The hazard of switching to ARB was greater in people with asthma (HR1.16, 95%CI 1.14-1.18, p=<0.001) and highest in those at BTS step ≥3 (HR1.35, 95%CI 1.32-1.39 and 1.18, 95%CI 1.15-1.22, p=<0.001 for patients aged ≥60 years and <60 years respectively). Hazard was highest with enalapril (HR1.25, 95%CI 1.18-1.34, p=<0.001; HR1.44, 95%CI 1.32-1.58, p=<0.001 for BTS step ≥3 asthma). No increased hazard was observed in COPD or those younger than 60 years at BTS step 1/2. The NNT varied by age, gender and BMI ranging between 21 and 4, being lowest in older women with BMI ≥25.

Conclusions: People with active asthma are more likely to switch to ARBs after commencing ACEI therapy. The NNT varies by age, gender, BMI and BTS step. ARBs could potentially be considered first-line in people with asthma and in those with high-risk characteristics.

Highlights box

1: What is already known on this topic?

- Many people are intolerant to ACE inhibitors due to cough and require switching to an angiotensin-II receptor blocker (ARB).
- ACE inhibitors may affect airway hyperresponsiveness in asthma, possibly mediated via bradykinin or cough reflex sensitivity.

2: What does this article add to our knowledge?

- People with asthma are generally at increased risk of switching to ARBs from ACEI therapy and is greatest in those with more severe asthma.
- The absolute risk of switching varies by age, sex and body mass index.

3: How does this study impact current management guidelines?

- ARBs could be considered first-line in older people with asthma or young people with more severe asthma including in those with other high-risk characteristics.

Key words

Asthma

Angiotensin converting enzyme

Cough

Epidemiology

Hypertension

Abbreviations

ACEI	Angiotensin converting enzyme inhibitor
AHR	Airway hyper-responsiveness
ARB	Angiotensin-II receptor blocker
BMI	Body mass index
BTS	British Thoracic Society treatment step
COPD	Chronic obstructive pulmonary disease
CVS	Cardiovascular
GP	General Practitioner
HR	Hazard ratio
ICS	Inhaled corticosteroids
LABA	Long-acting beta2-agonists
LKTA	Leukotriene receptor antagonists
NNT	Number needed to treat
SABA	Short-acting beta2-agonists
UK	United Kingdom

INTRODUCTION

Asthma is a highly prevalent disease causing significant morbidity, mortality and healthcare cost.[1] Comorbidity in asthma is common, and 62.6% of people with asthma reported to have ≥1 comorbidity, and the likelihood of having coronary artery disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, hypertension, diabetes and chronic kidney disease are all significantly greater in people with asthma compared to the general population.[2,3] Angiotensin-converting enzyme inhibitors (ACEI) are commonly prescribed medicines indicated for the management of these chronic diseases.[4] ACEI block the enzyme responsible for converting the peptide hormone angiotensin-I to angiotensin-II, which stimulates aldosterone release and causes vasoconstriction. Whilst ACEI have beneficial effects in the management of these chronic diseases, many patients are intolerant of long-term ACEI the most common reason of which is a dry persistent cough. This adverse drug reaction is thought to occur in around 10% of people treated with ACEI and may be related to increased levels of bradykinin.[5] This adverse reaction is considered a class effect of ACEI, suggesting that even low doses may also alter bradykinin levels in susceptible patients.

In people who develop ACEI intolerance from cough it is recommended that patients are switched to angiotensin-II receptor blocker (ARB) therapy.[5] ARBs have similar properties to ACEI but do not cause a persistent dry cough. ARBs inhibit angiotensin-II in a highly selective manner via a mechanism which does not alter bradykinin levels. However, irrespective of the cause having to switch treatments increases healthcare resource utilisation, treatment burden, treatment disutility, and may delay in establishing effective preventative therapy for the underlying indication. Despite being an important health economic factor many drug formularies and guidelines still recommend first-line treatment with ACEIs usually on cost grounds.[6]

A key tenet in the pathogenesis of asthma is airway hyper-responsiveness (AHR) which can be affected by a variety of environmental stimuli.[7,8] Bradykinin is a pro-inflammatory mediator that can cause bronchoconstriction and lung inflammation.[9] It is therefore plausible that treatment with ACEI may exacerbate asthma symptoms through bradykinin accumulation leading to worsening AHR, which may in turn increase the incidence of cough and switching to ARBs.[10] However, there is limited evidence studying the effect of ACEI exposure in patients with asthma. The aim of this study was to 1) examine ACEI drug utilisation in people with asthma, 2) assess the association of switching to ARBs in people with asthma compared to the general population and 3) characterise patients at greater risk.

METHODS

Data source

The UK Clinical Practice Research Datalink (CPRD) GOLD database was used to identify a large UK cohort of people with active asthma. CPRD GOLD contains anonymised electronic medical records from >680 general practices covering >5 million people in the UK with linked health data about patient demographics, prescriptions, diagnoses, hospitalisations and deaths. Patients are broadly representative of the UK general population in terms of age, sex and ethnicity.[11] General practices and patients within CPRD GOLD are required to meet defined quality standards in order to contribute data, with diagnoses have high validity, including for asthma that has a positive predictive value for respiratory disease of around 90%.[12,13] It has also been deemed to meet regulatory requirements to be used in a regulatory context.[14]

Study cohort

An open cohort of adults aged 18 years and over was identified from January 1 1998 through to June 30 2014. This time period reflects the start of database availability and the latest data available at the time of data extraction. Patients were required to be registered with a general practice providing up-to-standard data for at least 1 year prior to cohort entry. The population was divided into patients with active asthma with the remainder forming the rest of the general population. People with active asthma were defined using a validated code list for asthma and the receipt of at least two asthma medications with cohort follow-up commencing at the latest of these dates.[13] Asthma medicines were defined by the use of: inhaled short-acting beta2-agonists (SABA); inhaled corticosteroids (ICS); inhaled long-acting beta2-agonists (LABA); oral leukotriene antagonists (LKTA); and oral methylxanthines.[15] To reduce the chance of misclassification, people with a diagnostic code for asthma who also had a diagnostic code for COPD, interstitial lung disease or bronchiectasis were excluded from the active asthma population. For examining drug utilisation, cohort exit (that results in right censoring) for all patients was defined as the earliest of the following: end of study period; deregistration from the general practice; date of last data collection from the general practice; or death. For the analysis examining the risk of switching to an ARB following ACEI initiation, cohort entry was additionally defined by the date of the incident ACEI prescription in people without any prior ACEI or ARB exposure and cohort exit was additionally defined by the date of switching to an ARB or 180 days after ACEI discontinuation if no ARB had been initiated. For the switching analysis, patients prescribed an ARB on or prior to the incident ACEI were excluded. To test the robustness of the potential mechanism relating to asthma we also examined this association in

patients with COPD who acted as a negative control population. Patients with COPD are expected to be unaffected by the underlying pathophysiological hypothesis targeting AHR and were identified also using a validated code list.[16]

Exposures

All ACEI and ARB prescriptions were identified for patients within the cohort. The date of incident ACEI therapy was defined as the first ever ACEI prescription occurring during cohort follow-up with no previous prescription at any point prior to this time. ACEI discontinuation was defined by the date of an ACEI prescription with no further ACEI prescription following at least six months of this date. Switching to an ARB was defined by an incident ARB prescription issued within six months of the ACEI discontinuation date, with the date of the ACEI discontinuation representing day 1 of this six month period of follow-up (Online Repository Figure E1). The list of ACEI and ARB drug codes are provided in the Online Repository Table E1. For people who switched, the maximal ACEI dose prescribed prior to switching was calculated. ACEI doses were standardised using ramipril equivalent doses (please see Online Repository Table E2).

Outcomes

The primary outcome was the relative hazard of switching from ACEI to ARB therapy in people with active asthma compared to the general population, with trends in ACEI initiation and switching to ARBs reported over the study period among the active asthma population. Patients could switch at any point after initiating ACEI therapy providing they met the definition of switching and had not been censored due to one of the cohort exit criteria.

Analysis

Trends in the quarterly prevalence of ACEI and ARB initiation and discontinuation were calculated for the active asthma population. The start of each quarter was defined as January 01, April 01, July 01 and October 01. The quarterly prevalence was age-standardised using the European standard population.[17] The cohort analysis used Cox proportional hazards regression to calculate hazard ratios (HR) for switching to an ARB after initiating ACEI therapy in people with asthma compared to the general population. Time in this time to event analysis was the difference in days between the date of the incident ACEI prescription and switching to an ARB or another cohort exit censoring event as described above. Routine checks of the proportional hazards assumption were conducted by examining log-log

plots. We used the entire population available to use within the database that met our criteria. Based upon a two-group survival analysis this cohort has 90% at alpha 0.01 to detect a difference in relative hazard of 1.05 or greater. The Cox model was adjusted for the following baseline confounders: age; sex; practice-level socioeconomic deprivation applied to the individual (defined by the Index of Multiple Deprivation categorised into quintiles); smoking status (categorised into smoker, ex-smoker and non-smoker); body mass index (BMI, categorised into <20, 20-24, ≥25); history of cardiovascular disease (CVS); and history of hypertension. We selected variables based upon a search in the literature, known differences in the characteristics of asthma patients and indications for ACEI. A full model was fitted with using all variables as main effects. The active asthma cohort was categorized into three groups according to baseline British Thoracic Society (BTS) asthma treatment step (1, 2 and ≥3) defined by prescribed asthma medication as a potential marker of severity and included in the model.[1] The cohort was stratified by the most frequently prescribed types of ACEI and analysed separately. Multiple imputation was used to impute missing data on BMI, deprivation and smoking status. The imputation model included all variables relating to clinical characteristics, medication exposure and switching events. Multiple imputation used fully conditional specification, with linear regression for continuous variables and logistic regression for categorical variables with five imputations analysed using Rubin's rules.[18] We performed a complete case analysis to assess the impact of multiple imputation as a sensitivity analysis. To calculate an absolute measure, the rate of switching per 1000 patients was first calculated in the general cohort population, and was then multiplied by the adjusted hazard ratio to calculate the expected number of switchers in asthma. The number of asthma patients needed to treat (NNT) with an ACEI for one person to switch to an ARB was then calculated by taking the reciprocal of this value. Data on absolute risk are presented stratified by age and sex as done elsewhere.[19,20]

RESULTS

The active asthma cohort consisted of 521,857 adults (57.8% female, mean age 39 years) of which 66,895 patients (12.8%) were prescribed ACEIs, 28,791 were prescribed ARBs (5.5%), and 16,203 were prescribed both (3.1%) individually at some point during cohort follow-up. Trends in ACEI and ARB prescribing are presented in the Online Repository Figure E2.

Among the entire population, a total of 642,336 patients initiating ACEIs were identified, of which 40,953 had active asthma (6.4%). The remainder formed the general population, of which 5.2% had COPD. Patient characteristics are shown in table 1. Fewer patients with active asthma were men, current smokers or had a history of CVS disease. The most commonly prescribed ACEIs were ramipril, followed by lisinopril, perindopril then enalapril. Overall, 17.4% of people with active asthma switched to an ARB following ACEI initiation compared to 14.6% from the general population. Among those who switched, the number of GP consultations and mean ramipril10-equivalent dose prior to switching were similar between the groups.

The hazard ratio for switching to an ARB in patients with active asthma was increased compared to the general population (HR 1.16, 95%CI 1.14-1.18) (table 2). In contrast it was decreased for patients with COPD (HR 0.89, 95%CI 0.87-0.91). When associations between other patient characteristics were examined, the hazard of switching to an ARB was greater in women compared to men (HR 1.46, 95%CI 1.45-1.47), with increasing age (HR 1.65, 95%CI 1.62-1.71 for patients ≥60 years) and in patients with BMI ≥25 (table 2). In contrast, the hazard of switching to an ARB was lower in patients with a history of smoking and in patients registered at general practices in more socioeconomically deprived areas.

The increased hazard of switching to an ARB with active asthma was similar when stratified by gender (HR 1.16, 95%CI 1.13-1.19 for men and HR 1.17, 95%CI 1.15-1.20 for women). Hazard ratios for switching to an ARB were greater among active asthma patients aged ≥60 years and among those at BTS step ≥3 (HR 1.35, 95%CI 1.32-1.39 and HR 1.18, 95%CI 1.15-1.22 for patients aged ≥60 years and <60 years respectively) (figure 1 and table 3). While the hazard ratio was elevated among asthma patients aged ≥60 years at BTS step 1 and 2, no increased hazard was observed for those aged <60 years. When stratified by the four most commonly prescribed ACEIs, the hazard ratio for switching to an ARB in patients with active asthma was consistently elevated for all ACEI types, being numerically largest with enalapril (HR 1.24, 95%CI 1.17-1.32) (table 4) and greatest in those at BTS step ≥3. Results of the

sensitivity analysis using a complete case analysis were in keeping with the main results (Online Repository Table E3).

The overall incidence of switching to an ARB in the general population was 148 per 1000 patients with an additional 24 per 1000 patients (95%CI 21-27) among people with active asthma. The NNT with an ACEI for one person to switch to an ARB varied by age, sex, BMI and asthma severity (table 5). The NNT in men with BMI <20 varied from 24 to 11 being lower with older patients at BTS step 3. Corresponding numbers for men with BMI of ≥25 were lower ranging from 12 to 6 respectively. The NNT similarly varied in women, ranging from 14 to 7 in women with BMI <20 and from 10 to 4 in women with BMI of ≥25, being lower in older patients at BTS step 3. Corresponding numbers for the general population are shown in the Online Repository Table E4.

Discussion

Summary of findings

We observed that people with active asthma have an increased risk of ACEI intolerance and switching to ARB therapy compared to the general population. This association was greatest in those with more severe asthma, with people above and below 60 years of age at BTS step ≥3 asthma having a 35% increased hazard versus 18% increased hazard respectively. The hazard of switching to an ARB was consistently elevated with all commonly prescribed ACEIs in our population and was largest following treatment with enalapril, with BTS step ≥3 patients having a 44% increased hazard. However, patients below 60 years of age at BTS step 1 or 2 asthma were not at increased risk. The number of asthma patients needed to treat with ACEI for one person to switch was also significantly influenced by age, sex and BMI, which ranged from 21 to 4, being lowest in older women with a BMI of ≥25 at BTS step 3.

Comparison with previous literature

AHR is an important determinant in the pathophysiology of asthma and is affected by a variety of stimuli such as methacholine and bradykinin that can cause bronchoconstriction,.[7,8] Whereas methacholine induces bronchoconstriction in normal and in asthmatic subjects, bradykinin-induced bronchoconstriction is predominantly observed in asthmatics, suggesting the effect of bradykinin is related to structural and/or to functional airway abnormalities that occur in asthma.[7] Bradykinin's potent bronchoconstrictor effect in asthmatic patients is thought to be mediated via an indirect mechanism related to the level of AHR and active airway inflammation.[9,10] Whilst the increased hazard of switching in people with active asthma, but not COPD, would be in keeping with a specific effect on AHR other mechanisms such as ACEI increasing cough reflex hypersensitivity, which is similarly associated with female gender, cannot be excluded.[21]

Indirect acting AHR is related to the degree of aeroallergen sensitisation and occurs independently of airway calibre or ICS use.[22] This in turn may explain why the effect of bradykinin due to ACEI may be specific for asthma but not COPD, in addition to the presence of type 2 inflammation in the former. This is because AHR is not a key feature in the pathogenesis of COPD perhaps unless patients have asthma-COPD overlap syndrome. Indeed, fixed airway remodelling in COPD may be one reason why a decreased hazard of switching was observed in this population. Our observation of increased ACEI intolerance in patients with BTS step 3 and above is likely explained by such patients have more severe disease. Having said that, AHR has been shown to be attenuated by drugs such as ICS, which would be more prevalent in

patients taking step 3/4 therapy.[23-25] Some studies have evaluated bronchial reactivity of captopril, ramipril and enalapril in asthma patients and showed no change in reactivity.[26-31] However, the cumulative number of patients from all of these studies is only n=71, which in addition to studies employing different methods (ie. histamine, bradykinin or methacholine challenges or simply measuring lung function) limits the generalisability of these findings.

Although several types of ACEIs are available for clinical use, it cannot be assumed they are all equally effective or safe without head to head comparisons. In our study the hazard of switching to ARB with enalapril was modestly larger in people with asthma compared to other ACEI. In a meta-analysis of randomized controlled trials, ACEI cough had higher rates in hypertension and lowest rates in heart failure suggesting these may differ by underlying cardiovascular condition.[32] Although differences among users of different ACEI types remains possible, we adjusted for several of these factors and saw a larger hazard ratio for hypertension compared to cardiovascular disease. Similarly, a network meta-analysis of 29 randomized placebo controlled trials of ACEI therapy in heart failure patients also found that enalapril had the highest incidence of cough, gastrointestinal discomfort, and greater deterioration in renal function compared to other ACEIs.[33]

An increased risk of cough or switching to ARB therapy in people with asthma has recently been reported.[32,34] However, no studies used an active asthma population, examined associations by asthma severity or type of ACEI, or provided information relating to ACEI dose or the rate of healthcare utilisation rate prior to switching. Meanwhile information on absolute risk is lacking but is necessary to guide robust health economic and clinical decision is making. Women in the general population are considered to have a 1.5 to 2.3-fold increased risk of switching to ARBs following ACEI therapy.[35-37] However, the impact of increasing age has been less consistently reported and there remains a paucity of data around the association with BMI.[38-40] We clearly show that all three characteristics are relevant for people with asthma and are strong determinants of the NNT.

Strengths and limitations

This study has several strengths and limitations. First we analysed a large clinical population identified using a validated data source and definitions. Although cough is by far the most common reason for ACEI intolerance and switching to an ARB we were unable to directly measure ACEI-induced cough as an outcome. This would be challenging as cough may not be recorded sufficiently well to distinguish

between cough related to ACEIs as opposed to another condition, particularly in patients with asthma. Whilst cough is the predominant reason for ACEI intolerance in the general population, we cannot exclude the possibility that other symptoms such as wheeze or dyspnoea may have occurred, which have been reported among asthma patients using ACEIs.[40] However, switching to an ARB after ACEI treatment is considered to be the best marker for identifying ACEI-induced adverse drug reactions in electronic databases, having a positive predictive value of up to 90.5% with cough being the most commonly reported adverse reaction.[42,43]

Whist there remains the potential for unmeasured confounding from potentially important unknown patient factors not included in our model, we used a negative control population by examining the association in patients with COPD. The null findings in patients with COPD provide additional evidence suggesting our observed association is causal and that the increased hazard of switching observed in people with active asthma are potentially related to changes in AHR due to bradykinin. However, these results may not be generalizable to people with the asthma-COPD overlap syndrome. It would be pertinent to further evaluate the putative impact of ACEI in patients with known AHR and markers of type 2 inflammation such as fractional exhaled nitric oxide and blood eosinophils, as well as total and specific IgE levels.[44,45]

Clinical implications

It is recognised that managing comorbidities in patients with asthma may be associated with additional risk.[46-49] When evaluated for the management of hypertension, ARBs are thought to have similar effects on blood pressure, mortality and CVS outcomes compared with ACEIs, yet fewer patients in the general population withdraw from clinical trials due to adverse effects when treated with ARBs compared to ACEIs.[50] Despite the potentially higher incidence of switching with enalapril, the largest determinant on absolute risk in people with asthma appeared to be a person's age, gender and BMI. Given the high prevalence of obesity in the population combined with increasing age of patients, such factors are important determinants for considering whether ARBs should be recommended as first line therapy. This would be particularly relevant in people with asthma, where discriminating ACEI-induced cough from symptoms of uncontrolled asthma may be complex, potentially leading to unnecessary asthma treatment if not immediately recognised. Many guidelines for the management of patients with cardiovascular disease still recommend ACEIs as first-choice therapy, reserving ARBs as an alternative when patients are intolerant to ACEIs. This has led to recent calls to change these recommendations

given the equal efficacy but fewer adverse reactions with ARBs.[51] This would potentially avoid unnecessary health care appointments, patient treatment disutility, and delays in establishing effective therapy for the underlying clinical condition.

In conclusion, our findings suggest that ACEIs are less well tolerated in people with asthma compared to the general population. The NNT is lower in asthma and in those with older age, are female and have a higher BMI. Consideration could potentially be given to recommending ARBs first-line in people with asthma or those with high risk characteristics when treatment with a renin-angiotensin system inhibitor is clinically indicated.

Contributions

DM and BJL conceived the idea. All authors were involved in the study design. HW and DM performed the analysis and DM is the guarantor for the study. All authors contributed to the interpretation of results, writing the manuscript and approved the final draft. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Disclaimer

The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as reflecting the views of any organisation.

Data sharing

No data are available for sharing. Data can be accessed according to CPRD's standard terms and conditions and payment for using the CPRD database.

Study registration

The study has been registered in the EU PAS Register (no. EUPAS35083) [www.encepp.eu)

Ethical approval

The study was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare products and Regulatory Agency (MHRA) (protocol 14_240R).

References

1. British Thoracic Society Scottish Intercollegiate Guidelines Network. British Guideline on the Management of Asthma. Thorax. 2008;63 Suppl 4:iv1-121.
2. Weatherburn CJ, Guthrie B, Mercer SW, Morales DR. Comorbidities in adults with asthma: Population-based cross-sectional analysis of 1.4 million adults in Scotland. Clin Exp Allergy. 2017 Oct;47(10):1246-1252.
3. Steppuhn H, Langen U, Keil T, Scheidt-Nave C. Chronic disease co-morbidity of asthma and unscheduled asthma care among adults: results of the national telephone health interview survey German Health Update (GEDA) 2009 and 2010. Prim Care Respir J. 2014 Mar;23(1):22-9.
4. Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press. http://wwwmedicinescompletecom (accessed 1 Aug 2015).
5. British Hypertension Society. Drug classes: Angiotensin Converting Enzyme (ACE) Inhibitors (online). https://bihsoc.org/wp-content/uploads/2017/11/Angiotensin-Converting-Enzyme-Final-2017.pdf Accessed 12 Dec 2019.
6. National Health Service Tayside Area Formulary. Available at: http://www.taysideformulary.scot.nhs.uk/chaptersSubDetails.asp?FormularySectionID=2&SubSectionRef=02.05&SubSectionID=A100 Accessed 12 Dec 2019.
7. Barnes PJ. Bradykinin and asthma. Thorax. 1992;47(11):979-83.
8. Fuller RW, Dixon CM, Cuss FM, Barnes PJ. Bradykinin-induced bronchoconstriction in humans. Mode of action. Am Rev Respir Dis. 1987Jan;135(1):176-80.
9. Polosa, R., and S. T. Holgate. 1990. Comparative airway responses to inhaled bradykinin, kallidin, and [des-Arg9] bradykinin in normal and asthmatic subjects. Am. Rev. Respir. Dis. 142:1367-1371.
10. Roisman GL, Lacronique JG, Desmazes-Dufeu N, Carré C, Le Cae A, Dusser DJ. Airway responsiveness to bradykinin is related to eosinophilic inflammation in asthma. Am J Respir Crit Care Med. 1996 Jan;153(1):381-90.
11. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, Smeeth L. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015 Jun;44(3):827-36.
12. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol. 2010;69(1):4-14.
13. Nissen F, Morales DR, Mullerova H, Smeeth L, Douglas IJ, Quint JK. Validation of asthma recording in the Clinical Practice Research Datalink (CPRD). BMJ Open. 2017 Aug 11;7(8):e017474.
14. Pacurariu A, Plueschke K, McGettigan P, et al. Electronic healthcare databases in Europe: descriptive analysis of characteristics and potential for use in medicines regulation [published correction appears in BMJ Open. 2019 Feb 22;8(11):e023090corr1]. BMJ Open. 2018;8(9):e023090.
15. Joint Formulary Committee. British National Formulary. Respiratory system – 3 (online) London: BMJ Group and Pharmaceutical Press. http://wwwmedicinescompletecom (accessed 1 Aug 2015).
16. Quint JK, Müllerova H, DiSantostefano RL, Forbes H, Eaton S, Hurst JR, Davis K, Smeeth L. Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD). BMJ Open. 2014 Jul 23;4(7):e005540.
17. Eurostat. Revision of the European Standard Population. 2013 Edition. Available at: https://ec.europa.eu/eurostat/documents/3859598/5926869/KS-RA-13-028-EN.PDF/e713fa79-1add-44e8-b23d-5e8fa09b3f8f Accessed 20/12/2019.
18. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res. 2007 Jun;16(3):219-42.

19. Morales DR, Flynn R, Kurz X. Addendum to: Relative and Absolute Risk of Tendon Rupture with Fluoroquinolone and Concomitant Fluoroquinolone/Corticosteroid Therapy: Population-Based Nested Case-Control Study. Clin Drug Investig. 2019 Jun;39(6):591-594.
20. Morales D, Pacurariu A, Slattery J, Pinheiro L, McGettigan P, Kurz X. Association Between Peripheral Neuropathy and Exposure to Oral Fluoroquinolone or Amoxicillin-Clavulanate Therapy. JAMA Neurol. 2019 Jul 1;76(7):827-833.
21. Fox AJ, Lalloo UG, Belvisi MG, Bernareggi M, Chung KF, Barnes PJ. Bradykinin-evoked sensitization of airway sensory nerves: a mechanism for ACE-inhibitor cough. Nat Med. 1996 Jul;2(7):814-7.
22. Currie GP, Jackson CM, Lee DK, Lipworth BJ. Allergen sensitization and bronchial hyper-responsiveness to adenosine monophosphate in asthmatic patients. *Clin Exp Allergy* 2003: 33(10): 1405-1408.
23. Currie GP, Jackson CM, Ogston SA, Lipworth BJ. Airway-stabilizing effect of long-acting beta2-agonists as add-on therapy to inhaled corticosteroids. *QJM : monthly journal of the Association of Physicians* 2003: 96(6): 435-440.
24. Currie GP, Lipworth BJ. Bronchoprotective effects of leukotriene receptor antagonists in asthma: A meta-analysis. *Chest* 2002: 122(1): 146-150.
25. Currie GP, Fowler SJ, Lipworth BJ. Dose response of inhaled corticosteroids on bronchial hyperresponsiveness: A meta-analysis. *Annals of Allergy, Asthma and Immunology* 2003: 90(2): 194-198.
26. Sala H, Abad J, Juanmiquel L, Plans C, Ruiz J, Roig J, et al. Captopril and bronchial reactivity. Postgrad Med J 1986;62(suppl 1):76-7.
27. Riska H, Stenius-Aarniala B, Sovijarvi AR. Comparison of the effects of an angiotensin converting enzyme inhibitor and a calcium channel blocker on blood pressure and respiratory function in patients with hypertension and asthma. J Cardiovasc Pharmacol 1987;10(suppl 10):S79-81.
28. Riska H, Sovijarvi AR, Ahonen A, Salorinne Y, Sundberg S, Stenius-Aarniala B. Effects of captopril on blood pressure and respiratory function compared to verapamil in patients with hypertension and asthma. J Cardiovasc Pharmacol 1990;15:57-61.
29. Kaufman J, Schmitt S, Barnard J, Busse W. Angiotensin-converting enzyme inhibitors in patients with bronchial responsiveness and asthma. Chest 1992;101:922-5.
30. Mue S, Tamura G, Yamauchi K, Fujimoto Y, Inoue H, Takishima T. Bronchial responses to enalapril in asthmatic, hypertensive patients. Clin Ther 1990;12:335- 43.
31. Dixon CM, Fuller RW, Barnes PJ. The effect of an angiotensin converting enzyme inhibitor, ramipril, on bronchial responses to inhaled histamine and bradykinin in asthmatic subjects. Br J Clin Pharmacol. 1987 Jan;23(1):91-3. doi: 10.1111/j.1365-2125.1987.tb03015.x.
32. Vukadinović D, Vukadinović AN, Lavall D, Laufs U, Wagenpfeil S, Böhm M. Rate of Cough During Treatment With Angiotensin-Converting Enzyme Inhibitors: A Meta-Analysis of Randomized Placebo-Controlled Trials. Clin Pharmacol Ther. 2019 Mar;105(3):652-660.
33. Sun W, Zhang H, Guo J, Zhang X, Zhang L, Li C, Zhang L. Comparison of the Efficacy and Safety of Different ACEIs in Patients With Chronic Heart Failure: A PRISMA-Compliant Network Meta-Analysis. Medicine (Baltimore). 2016 Feb;95(6):e2554.
34. Mahmoudpour SH, Asselbergs FW, Souverein PC, de Boer A, Maitland-van der Zee AH. Prescription patterns of angiotensin-converting enzyme inhibitors for various indications: A UK population-based study. Br J Clin Pharmacol. 2018 Oct;84(10):2365-2372.

35. Humbert X, Alexandre J, Sassier M, Default A, Gouraud A, Yelehe-Okouma M,Puddu PE, Fedrizzi S. Long delay to onset of ACEIs-induced cough: Reason of difficult diagnosis in primary care? Eur J Intern Med. 2017 Jan;37:e50-e51.
36. Brugts JJ, Arima H, Remme W, Bertrand M, Ferrari R, Fox K, DiNicolantonio J,MacMahon S, Chalmers J, Zijlstra F, Caliskan K, Simoons ML, Mourad JJ, Boersma E, Akkerhuis KM. The incidence and clinical predictors of ACE-inhibitor induced dry cough by perindopril in 27,492 patients with vascular disease. Int J Cardiol. 2014 Oct 20;176(3):718-23.
37. Mahmoudpour SH, Baranova EV, Souverein PC, Asselbergs FW, de Boer A, Maitland-van der Zee AH; PREDICTION-ADR consortium. Determinants of angiotensin-converting enzyme inhibitor (ACEI) intolerance and angioedema in the UK Clinical Practice Research Datalink. Br J Clin Pharmacol. 2016 Dec;82(6):1647-1659.
38. Morimoto T, Gandhi TK, Fiskio JM, Seger AC, So JW, Cook EF, Fukui T, Bates DW. An evaluation of risk factors for adverse drug events associated with angiotensin-converting enzyme inhibitors. J Eval Clin Pract. 2004 Nov;10(4):499-509.
39. Alharbi FF, Kholod AAV, Souverein PC, Meyboom RH, de Groot MCH, de Boer A, Klungel OH. The impact of age and sex on the reporting of cough and angioedema with renin-angiotensin system inhibitors: a case/noncase study in VigiBase. Fundam Clin Pharmacol. 2017 Dec;31(6):676-684.
40. Jamshed F, Jaffry H, Hanif H, Kumar V, Naz U, Ahmed M, Fareed S. Demographic and Clinical Characteristics of Patients Presenting With Angiotensin-converting Enzyme Inhibitors Induced Cough. Cureus. 2019 Sep 11;11(9):e5624.
41. Fox AJ, Lalloo UG, Belvisi MG, Bernareggi M, Chung KF, Barnes PJ. Bradykinin-evoked sensitization of airway sensory nerves: a mechanism for ACE-inhibitor cough. Nat Med. 1996 Jul;2(7):814-7.
42. Mahmoudpour SH, Asselbergs FW, de Keyser CE, Souverein PC, Hofman A, Stricker BH, de Boer A, Maitland-van der Zee AH. Change in prescription pattern as a potential marker for adverse drug reactions of angiotensin converting enzyme inhibitors. Int J Clin Pharm. 2015 Dec;37(6):1095-103.
43. Speirs C, Wagniart F, Poggi L. Perindopril postmarketing surveillance: a 12 month study in 47,351 hypertensive patients. Br J Clin Pharmacol. 1998 Jul;46(1):63-70.
44. Kuo CR, Spears M, Haughney J, Smith A, Miller J, Bradshaw T, Murray L, Williamson P, Lipworth B. Scottish consensus statement on the role of FeNO in adult asthma. *Respir Med* 2019: 155: 54-57.
45. Price DB, Bosnic-Anticevich S, Pavord ID, Roche N, Halpin DMG, Bjermer L, Usmani OS, Brusselle G, Ming SWY, Rastogi S. Association of elevated fractional exhaled nitric oxide concentration and blood eosinophil count with severe asthma exacerbations. *Clin Transl Allergy* 2019: 9: 41.
46. Morales DR, Lipworth BJ, Donnan PT, Jackson C, Guthrie B. Respiratory effect of beta-blockers in people with asthma and cardiovascular disease: population-based nested case control study. BMC Med. 2017 Jan 27;15(1):18.
47. Morales DR, Dreischulte T, Lipworth BJ, Donnan PT, Jackson C, Guthrie B. Respiratory effect of beta-blocker eye drops in asthma: population-based study and meta-analysis of clinical trials. Br J Clin Pharmacol. 2016 Sep;82(3):814-22.
48. Morales DR, Guthrie B, Lipworth BJ, Jackson C, Donnan PT, Santiago VH. NSAID-exacerbated respiratory disease: a meta-analysis evaluating prevalence, mean provocative dose of aspirin and increased asthma morbidity. Allergy. 2015 Jul;70(7):828-35.
49. Morales DR, Jackson C, Lipworth BJ, Donnan PT, Guthrie B. Adverse respiratory effect of acute β-blocker exposure in asthma: a systematic review and meta-analysis of randomized controlled trials. Chest. 2014 Apr;145(4):779-786.

50. Li EC, Heran BS, Wright JM. Angiotensin converting enzyme (ACE) inhibitors versus angiotensin receptor blockers for primary hypertension. Cochrane Database Syst Rev. 2014 Aug 22;(8):CD009096.
51. Messerli FH, Bangalore S, Bavishi C, Rimoldi SF. Angiotensin-Converting Enzyme Inhibitors in Hypertension: To Use or Not to Use? J Am Coll Cardiol. 2018 Apr 3;71(13):1474-1482.

Table 1. Demographic details and baseline covariates of people initiating ACEI therapy in the general population and in those with active asthma.

Patient characteristics	Active asthma cohort (n = 40953)	General population (n = 601383)
Mean age, (SD)	58.7 (13.3)	64.4 (13.8)
Male sex (%)	17274 (42.2)	315463 (52.5)
Mean years of follow-up (SD)	3.0 (3.3)	3.3 (3.4)
Mean BMI at baseline (SD)	30.7 (6.7)	28.7 (5.9)
Missing BMI (%)	1314 (3.2)	39519 (6.6)
Practice level deprivation (%):		
1 (least deprived)	3712 (8%)	55612 (9.3)
2	5510 (14%)	81311 (13.5)
3	5273 (13%)	79094 (13.2)
4	5329 (13%)	87680 (14.6)
5 (most deprived)	5115 (13%)	77959 (13.0)
Missing	16014 (39.1)	219727 (36.5)
COPD (%)	0 (0)	31294 (5.2)
Hypertension (%)	27783 (67.8)	401,918 (66.8)
Cardiovascular disease (%)	8090 (19.8)	169805 (28.2)
Baseline smoking status (%)		
Non-smoker	20918 (55.7)	256732 (49.2)
Ex-smoker	11537 (30.7)	167358 (32.1)
Current smoker	5129 (13.7)	98001 (18.8)
Missing smoking status (%)	3369 (8.2)	79292 (13.2)
ACEI type (%)		
Ramipril	22600 (55.2)	324942 (54.0)
Lisinopril	10279 (25.1)	148389 (24.7)
Perindopril	5741 (14.0)	91054 (15.1)
Enalapril	1907 (4.7)	28760 (4.8)
Other*	426 (1.0)	8238 (1.4)
Number discontinuing ACEIs (%)	18973 (46.3)	271773 (45.2)
Number switching to an ARB (%)	7108 (17.4)	88980 (14.8)
Mean ACEI dose mg (SD)*	4.4 (2.9)	4.5 (3.0)
Mean no. GP consultations (SD)**	12.4 (21.1)	12.0 (18.9)

*Other = quinapril, trandolapril, captopril, fosinopril, imidapril, cilazapril or moexipril. **Standardised ramipril equivalent dose prior to switching. ***Mean number of general practice (GP) surgery consultations between the date of ACEI initiation and ARB initiation. SD=standardised difference. P-value for all comparisons <0.05 using Chi-square test for counts and t-test for continuous variables.

513 Table 2. Hazard ratios for switching to an ARB following any ACEI therapy in people with active asthma compared to
514 the general population and other risk factors.

	Crude Hazard ratio (95% CI)	Crude P-value	Adjusted Hazard ratio (95% CI)	Adjusted P-value
Population				
General population	1.00		1.00	
Active asthma	1.22 (1.20-1.24)	<0.001	1.16 (1.14–1.18)	<0.001
COPD	0.79 (0.78-0.81)	<0.001	0.89 (0.87-0.91)	<0.001
Hypertension	1.34 (1.33-1.35)	<0.001	1.21 (1.20–1.22)	<0.001
Cardiovascular disease	0.81 (0.80-0.82)	<0.001	0.88 (0.87-0.89)	<0.001
Sex				
Male	1.00		1.00	
Female	1.53 (1.52-1.54)	<0.001	1.46 (1.45-1.47)	<0.001
Age at baseline				
<40	1.00		1.00	
40-49	1.34 (1.30-1.37)	<0.001	1.32 (1.29-1.36)	<0.001
50-59	1.53 (1.50-1.57)	<0.001	1.53 (1.49-1.57)	<0.001
>60	1.67 (1.63-1.71)	<0.001	1.66 (1.62-1.70)	<0.001
BMI category				
<20	1.00		1.00	
20-24	1.37 (1.34-1.40)	<0.001	1.43 (1.39-1.46)	<0.001
>=25	1.52 (1.49-1.56)	<0.001	1.55 (1.51-1.59)	<0.001
Smoking status				
Non-smoker	1.00		1.00	
Ex-smoker	0.89 (0.88-0.90)	<0.001	0.96 (0.95–0.97)	<0.001
Current smoker	0.64 (0.63-0.65)	<0.001	0.73 (0.72–0.74)	<0.001
Deprivation				
1 (Least deprived)	1.00		1.00	
2	1.07 (1.05-1.08)	<0.001	1.05 (1.04-1.06)	<0.001
3	1.13 (1.12-1.14)	<0.001	1.10 (1.09-1.11)	<0.001
4	1.17 (1.15-1.18)	<0.001	1.13 (1.12-1.15)	<0.001
5 (Most deprived)	1.24 (1.22-1.25)	<0.001	1.20 (1.18-1.21)	<0.001

515 BTS step=British Thoracic Society asthma treatment step. Adjusted model adjusted for gender, age, BMI, smoking
516 status, history of hypertension, cardiovascular disease, COPD and socioeconomic deprivation. Deprivation=Index of
517 multiple deprivation. CI=confidence interval.

518 Table 3. Overall adjusted cause-specific hazard ratios for switching to an ARB following ACEI therapy stratified by
519 British Thoracic Society asthma treatment step.

BTS asthma treatment step	Number with asthma (%)	Crude cause-specific Hazard ratio (95% CI)	Crude P value	Adjusted cause-specific Hazard ratio (95% CI)	Adjusted P value
Age >=60 years					
≥3	9057 (45.6)	1.47 (1.44-1.51)	<0.001	1.35 (1.32-1.39)	<0.001
2	5774 (29.1)	1.22 (1.18-1.26)	<0.001	1.13 (1.09-1.17)	<0.001
1	5026 (25.3)	1.23 (1.19-1.28)	<0.001	1.14 (1.09-1.19)	<0.001
Age <60 years					
≥3	9398 (44.6)	1.27 (1.23-1.30)	<0.001	1.18 (1.15-1.22)	<0.001
2	4982 (23.6)	1.09 (1.05-1.14)	<0.001	1.02 (0.96-1.07)	0.753
1	6716 (31.8)	0.97 (0.94-1.01)	0.193	0.96 (0.92-1.00)	0.146

520 BTS step=British Thoracic Society asthma treatment step. Adjusted model adjusted for gender, age, BMI, smoking status,
521 history of hypertension, history of cardiovascular disease, COPD and socioeconomic deprivation. CI=confidence interval.

522 Table 4. Overall adjusted cause-specific hazard ratios for switching to an ARB following different types of ACEI
523 therapy.

ACEI type	Crude Hazard ratio (95% CI)	Crude P value	Adjusted Hazard ratio (95% CI)	Adjusted P value
Enalapril				
BTS step ≥3	1.51 (1.39-1.64)	<0.001	1.44 (1.32-1.58)	<0.001
BTS step 2	1.29 (1.16-1.42)	<0.001	1.21 (1.08-1.35)	<0.001
BTS step 1	1.04 (0.92-1.17)	0.582	1.01 (0.89-1.16)	0.841
Overall	1.31 (1.24-1.39)	<0.001	1.25 (1.18-1.34)	<0.001
Ramipril				
BTS step ≥3	1.34 (1.30-1.37)	<0.001	1.27 (1.23-1.30)	<0.001
BTS step 2	1.16 (1.12-1.20)	<0.001	1.09 (1.05-1.14)	<0.001
BTS step 1	1.05 (1.01-1.09)	0.010	1.04 (1.00-1.08)	0.060
Overall	1.21 (1.19-1.24)	<0.001	1.16 (1.14-1.19)	<0.001
Lisinopril				
BTS step ≥3	1.32 (1.27-1.37)	<0.001	1.26 (1.21-1.31)	<0.001
BTS step 2	1.14 (1.08-1.19)	<0.001	1.09 (1.04-1.15)	0.001
BTS step 1	1.10 (1.04-1.16)	<0.001	1.10 (1.05-1.17)	<0.001
Overall	1.21 (1.18-1.24)	<0.001	1.17 (1.14-1.21)	<0.001
Perindopril				
BTS step ≥3	1.36 (1.30-1.43)	<0.001	1.27 (1.21-1.33)	<0.001
BTS step 2	1.09 (1.01-1.17)	0.026	1.03 (0.95-1.11)	0.456
BTS step 1	1.01 (0.93-1.09)	0.856	0.97 (0.89-1.05)	0.410
Overall	1.20 (1.16-1.25)	<0.001	1.13 (1.09-1.18)	<0.001

524 BTS step=British Thoracic Society asthma treatment step. Adjusted model adjusted for gender, age, BMI, smoking
525 status, history of hypertension, cardiovascular disease, COPD and socioeconomic deprivation. ACE=angiotensin
526 converting enzyme inhibitor. CI=confidence interval.

Table 5. Number of asthma patients needed to treat with an ACEI for one person to switch to an ARB according to age, sex, BMI and asthma severity.

	Men				Women			
	Rate in non-asthmatics per 1000	NNT Step 1 Asthma	NNT Step 2 Asthma	NNT Step ≥3 Asthma	Rate in non-asthmatics per 1000	NNT Step 1 Asthma	NNT Step 2 Asthma	NNT Step ≥3 Asthma
BMI <20								
Age <40 years	9	24	24	21	74	14	14	11
Age 40-59 years	63	16	16	14	126	8	8	7
Age >=60 years	68	13	13	11	114	8	8	7
BMI 20-24								
Age <40 years	63	16	16	14	99	10	10	9
Age 40-59 years	91	11	11	9	149	7	7	6
Age >=60 years	114	8	8	7	176	5	5	4
BMI >=25								
Age <40 years	82	12	12	10	101	10	10	8
Age 40-59 years	118	9	9	7	171	6	6	5
Age >=60 years	135	7	7	6	192	5	5	4

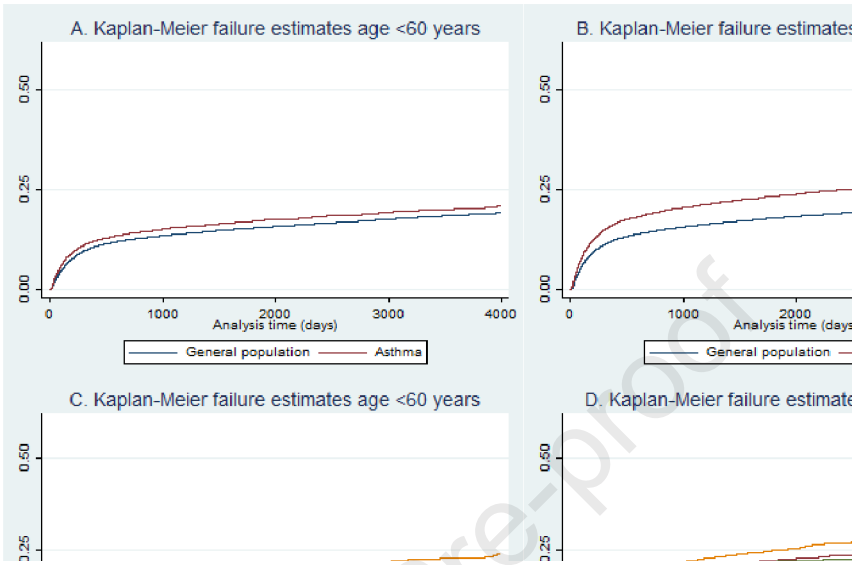
Rate=Rate of switching to an ARB following ACEI initiation. BMI=Body mass index. NANT=Number with asthma needed to treat with ACEI for a switch to ARB to occur. NNT calculated taking the reciprocal of rate in non-asthma population*hazard ratio of switching in asthma by age and BTS step, rounded to the nearest whole number. Step=British Thoracic Society asthma treatment step.

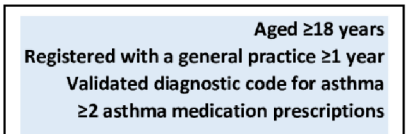
538 **Figure Legends**

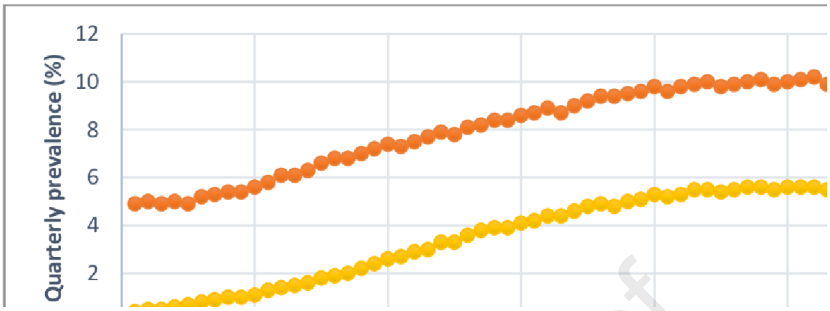
539

540 **Figure 1. Kaplan-Meier failure plots for risk of switching to an ARB following treatment with ACEI in A) people**
541 **under 60 years with asthma, B) people under 60 years by BTS treatment step, C) people aged 60 years or older**
542 **with asthma, and D) people aged 60 years or older by BTS treatment step.**

543







Supplementary Figure Legends

Figure E1. Diagram demonstrating the exposure windows used to define switching to ARB therapy following initiation of ACEI therapy.

Figure E2. Age-standardized quarterly prevalence of ACEIs and ARBs in patients with active asthma.

ACE=angiotensin converting-enzyme inhibitor. ARB=angiotensin-II receptor blocker. Q=quarter.